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APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
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EXAMINER	
YAO, LEI	

ART UNIT	PAPER NUMBER
1642	

DATE MAILED: 11/17/2005

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	10/779,476	LEONI, LORENZO M.	
	Examiner	Art Unit	
	Lei Yao, Ph.D.	1642	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *11 October 2005*.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *1-46,48-61,66,67 and 72-80* is/are pending in the application.

4a) Of the above claim(s) *13-42,48-50,59,60* is/are withdrawn from consideration.

5)☐ Claim(s) *9,10,51,61,66,67,72-76 and 79* is/are allowed.

6)☒ Claim(s) *1-4,6-8,11,12,43-45,52-55, 57,58 ,77-78, 80* is/are rejected.

7)☐ Claim(s) *5,46 and 56* is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date *1/12/05*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Applicant's elections of Group I (1-12, 43-46, 51-61, 66-67, and 72-80) and species of mesothelionma in the reply filed on 10/11/2005 are acknowledged. Because applicant did not distinctly and specifically point out the supposed errors in the restriction requirement, the election has been treated as an election without traverse (MPEP § 818.03(a)).

Claims 47, 62-65 and 68-71 have been cancelled. Claim 61 has been amended. Claims 1-46, 48-61, 66-67, 72-80 are pending. Claims 13-42, 48-50 and 59-60 are withdrawn from further consideration by the examiner, 37 CFR 1.142(b), as being drawn to a non-elected invention and species. Claims 1-12, 43-46, 51-58, 61, 66-67, and 72-80 are examined on the merits.

Information Disclosure Statement

The information disclosure statement (s) (IDS) submitted on 1/13/05 are/is considered by the examiner and initialed copy of the PTO-1449 is enclosed.

Claim Objection

Claims1-5 and 52-56 are objected to under 37 CFR 1.75 as being a substantial duplicate of claims 1-5. When two claims in an application are duplicates or else are so close in content that they both cover the same thing, despite a slight difference in wording, it is proper after allowing one claim to object to the other as being a substantial duplicate of the allowed claim. See MPEP § 706.03(k). Appropriate correction or cancellation of the claims is required.

Claim Rejections - 35 USC § 112

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

As drawn to scope of enablement-Binding Agent

Claims 1, 6-8, 43, 52 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for monoclonal antibody produced by hybridoma cell line ATCC PTA-5001, does not reasonably provide enablement for other MTAP-binding agent. The specification does not enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to use and make the invention commensurate in scope with these claims.

The factor considered when determining if the disclosure satisfies the enablement requirement and whether any is undue include, but are not limited to: 1) nature of the invention, 2) state of the prior art, 3) relative skill of those in the art, 4) level of predictability in the art, 5) existence of working examples, 6) breadth of necessary experimentation claims, 7) amount of direction or guidance by the inventor, and 8) quantity of experimentation needed to make or use the invention. *In re wands,* 858 F.2d 731, 737.8 USPQ2d 1400, 1404 (Fed. Cir.1988).

The claims are broadly drawn to MTAP-binding agent that specifically binds to human MTAP protein in an embedded biological sample, which is not embedded in OCT compound. The specification on page 11 teaches that term "MTAP-binding agent" refer to molecules that bind with specificity to human MTAP protein or a fragment thereof. The molecule may be a **polymer, chemical reagent, an antibody, as defined herein, and other MTAP-binding proteins.** However, the specification teaches only one MTAP binding agent, an monoclonal antibody, which binds to MTAP-expressing cell lines, human non-small cell lung carcinoma cell A427 and leukemia MOLT-4, not MTAP-deleted cells, such as Jurkat and lung cancer A549 (page 68, para 2). The specification neither discloses particular functional or structural attributes of an MTAP-binding agent, nor a working example of MTAP-binding agent to bind to MTAP protein or MTAP-expressing cells or tissues except the monoclonal anti-MTAP antibody set forth above. Therefore, one skilled in the art would not know how to use the claimed MTAP-binding agent other than an antibody based on the teachings in the prior art or instant specification.

As the specification set forth above, the MTAP-binding agent may be a polymer, chemical reagent, an antibody, as defined herein, and other MTAP-binding proteins, which include multitude of compounds that are structurally unrelated. Applicants have not provided any guidance as to how the

MTAP-binding agents interact with MTAP protein, nor have the applicants determined minimal structure required by the agent to bind to MTAP protein except the monoclonal anti-MTAP antibody. In the absence of this relationship between the structure and binding activity, applicant would have to screen million of compounds including a polymer, chemical reagent, or any other test compound to determine which has the ability to bind MTAP protein.

In view of the lack of guidance, lack of examples, and lack of predictability associated with regard to the activity of claimed MTAP-binding agent binding of the MTAP protein, one skilled in the art would be forced into under experimentation in order to practice the broadly claimed invention.

As drawn to written description-Binding to MTAP Epitope

Claims 11-12 and 80 are rejected under 35 U.S.C. 112, first paragraph, as failing to comply with the written description requirement. The claim(s) contains subject matter which was not described in the specification in such a way as to reasonably convey to one skilled in the relevant art that the inventor(s), at the time the application was filed, had possession of the claimed invention.

The claims are drawn to a genus of grafted antibodies and functional fragments thereof, the members of which have specific binding activity for "MTAP epitope as to a monoclonal antibody produced by a cell line PTA-5001 (MTAP epitope)".

The specification does not describe with any degree of particularity a single member of the genus of "MTAP epitope" to which the members of the claimed genus of antibodies must bind, such that the specification might reasonably convey to the skilled artisan that Applicant had possession of the claimed invention at the time the application was filed. At page 13, paragraph 4, the specification describes, "Antibodies specific for a particular human MTAP epitope may recognize proteins highly similar to the MTAP protein". However, given this definition of "a antibody", one skilled in the art could not immediately recognize or distinguish members of the genus of claimed antibodies capable of binding such an epitope, because one could not immediately recognize or distinguish members of the genus of MTAP epitopes to which the members of the claimed genus of antibodies must bind.

The Guidelines for Examination of Patent Applications Under the 35 U.S.C. 112, paragraph 1, Written Description" Requirement (66 FR 1099-1111, January 5, 2001) state, "possession may be shown in a variety of ways including description of an actual reduction to practice, or by showing the invention was 'ready for patenting' such as by disclosure of drawings or structural chemical formulas that show that the invention was complete, or by describing distinguishing identifying characteristics sufficient to show that the applicant was in possession of the claimed invention" (*Id.* at 1104). Moreover, because the claims encompass a genus of variant species, an adequate written description of the claimed invention must include sufficient description of at least a representative number of species by actual reduction to practice, reduction to drawings, or by disclosure of relevant, identifying characteristics sufficient to show that Applicant was in possession of the claimed genus. However, factual evidence of an actual reduction to practice has not been disclosed by Applicant in the specification; nor has Applicant shown the invention was "ready for patenting" by disclosure of drawings or structural chemical formulas that show that the invention was complete; nor has Applicant described distinguishing identifying characteristics sufficient to show that Applicant were in possession of the claimed invention at the time the application was filed.

As evidenced by Greenspan et al. (*Nature Biotechnology* **7**: 936-937, 1999), defining epitopes is not as easy as it seems. Greenspan et al. recommends defining an epitope by the structural characterization of the molecular interface between the antigen and the antibody is necessary to define an "epitope" (page 937, column 2). According to Greenspan et al., an epitope will include residues that make contacts with a ligand, here the antibody, but are energetically neutral, or even destablilizing to binding. Furthermore, an epitope will not include any residue not contacted by the antibody, even though substitution of such a residue might profoundly affect binding. Accordingly, it follows the epitope to which any given antibody binds can only be identified empirically. Even using a competition assay, the skilled artisan cannot determine whether an antibody binds the same epitope as another antibody because an antibody that competes with another does not necessarily bind the same epitope as the other; rather, one antibody may bind a spatially overlapping epitope to sterically hinder binding of the other. Therefore, absent a detailed and particular description of a representative number, or at least a substantial number of the members of the genus of epitopes to which the members of the claimed genus of antibodies must

bind, the skilled artisan could not immediately recognize or distinguish members of the claimed genus of antibodies. Moreover, since the specification has not identified which amino acids of the genus of epitopes of the denatured collagen molecules to which the members of the claimed genus of antibodies must bind, which are critical or essential to the binding, one skilled in the art would not recognize that Applicant had possession of the claimed invention at the time the application was filed.

Claim Rejections - 35 USC § 102

1. The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (e) the invention was described in (1) an application for patent, published under section 122(b), by another filed in the United States before the invention by the applicant for patent or (2) a patent granted on an application for patent by another filed in the United States before the invention by the applicant for patent, except that an international application filed under the treaty defined in section 351(a) shall have the effects for purposes of this subsection of an application filed in the United States only if the international application designated the United States and was published under Article 21(2) of such treaty in the English language.

Claims 1-4, 11-12, 52-55, and 57-58 are rejected under 35 U.S.C. 102(e) as being anticipated by Carson et al., (US Patent Application Publication, US2004/0096436, effective filing date, Aug 2, 2002).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

The set of the claims are drawn to an MTAP-binding agent that specifically binds to human methylthioadenosine phosphorylase (MTAP) protein in an embedded biological sample, comprising polyclonal and monoclonal antibody for MTAP and a kit containing the antibody for MTAP-binding agent or antibody.

Carson et al., disclose monoclonal and polyclonal antibodies, which specifically bind to MTAP polypeptide (para 105 and 108). Carson et al., further disclose that the antibodies are used to detect

MTAP in immuno-blot assays including immunohistochemical assays on physiological sample (para 114). It is inherent that the antibody of Carson et al., have binding affinities greater than 10^5 M^{-1}.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

The factual inquiries set forth in *Graham* **v.** *John Deere Co.*, 383 U.S. 1, 148 USPQ 459 (1966), that are applied for establishing a background for determining obviousness under 35 U.S.C. 103(a) are summarized as follows:

1. Determining the scope and contents of the prior art.
2. Ascertaining the differences between the prior art and the claims at issue.
3. Resolving the level of ordinary skill in the pertinent art.
4. Considering objective evidence present in the application indicating obviousness or nonobviousness.

1. Claims 43-45 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carson et al., (US Patent Application Publication, US2004/0096436, effective filing date, Aug 2, 2002.) as applied to claims 1-4, 11-12, 52-55 above, and further in view of Medenica et al., (US Patent 5744585, April, 1998)

Claims 43-45 are drawn to a kit comprising an MTAP-Binding agent or antibody for MTAP that specifically binds with an embedded human MTAP protein.

The teaching by Carson et al., are set forth above.

Carson et al., do not teach a kit comprising MTAP-Binding agent or antibody for MTAP.

Formation of a kit and making a pharmaceutical composition using known component comprising pharmaceutically acceptable carrier is within the purviews of one skilled in the art.

For example, Medenica et al., teach a kit comprising antibody and a method of the antibody to bind to the antigen (column 13, line 5-10).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed

invention was made to use MTAP-Binding agent or antibody for MTAP as taught by Carson et al., as an active pharmaceutical composition and making kit as taught by Carson et al., with the expected benefit for use MTAP-Binding agent or antibody for MTAP to bind to an embedded human MTAP protein to form a complex. One of ordinary skill in the art would have been motivated to combine the teachings of Carson et al., to the teaching of Medenica et al., to make a kit containing MTAP-Binding agent or antibody for MTAP because Carson et al., have shown a antibody for MTAP and Medenica et al., have shown a kit including antibody as an activate component for detecting a tumor-associated antigen and a method of use the kit for diagnosis for a cancer.

2. Claims 1-4, 6-8, 11-12, 52-55, 57-58, 77-78 are rejected under 35 U.S.C. 103(a) as being unpatentable over Carson et al., (US Patent Application Publication, US2004/0096436, effective filing date, Aug 2, 2002.) in view of Mulshine et al., (US Patent 4569788, Feb, 1986).

Claims 1-4, 11-12, and 52-55, 57-58 are set forth above. Claims 6-8, 53-55 are further drawn to claim 1 or claims 52, wherein the embedded biological sample is fixed with formalin and embedded in paraffin. Claims 11-12 are drawn to a monoclonal antibody which bind to the same human MTAP epitope as monoclonal antibody produce by hybridoma cell PTA-5001.

The teaching by Carson et al., are set forth above.

Carson et al., do not teach embedded biological sample is embedded in paraffin and fixed in formalin.

Mulshine et al., teach that biological sample, such as autopsy tissue, is fixed in formalin and embedded in paraffin. Mulshine et al., teach an antibody detecting an antigen presented in the embedded tissue through immunohistochemical staining (column 6, pare 3).

It would have been prima facie obvious to one of ordinary skill in the art at the time the claimed invention was made to make an antibody comprising MTAP-Binding agent or antibody for MTAP binding to MTAP presented in the formalin fixed, paraffin embedded tissue as taught by Carson et al., and Carson et al., with the expected benefit for MTAP binding and detecting MTAP in the paraffin embedded human

tissue comprising a tumor tissues. One of ordinary skill in the art would have been motivated to combine the teachings of Carson et al., to the teaching of Mulshine et al., to make the MTAP-Binding agent comprising an antibody for MTAP detection in the paraffin embedded tissues including tumor autopsy tissues because Carson et al., have shown an antibody for MTAP and Mulshine et al., al., have shown a antibody used for detecting tumor-associated antigen in the formalin fixed and paraffin embedded tissues not frozen tissue embedded in OCT.

Claim Objections

Claim 46 is objected to as being dependent upon a rejected base claim, but would be allowable if rewritten in independent form including all of the limitations of the base claim and any intervening claims.

Conclusion

Claims 9-10, 51, 61, 66-67, 72-76, and 79 are allowed.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Lei Yao, Ph.D. whose telephone number is 571-272-3112. The examiner can normally be reached on 8am-4.30pm Monday to Friday.

Any inquiry of a general nature, matching or file papers or relating to the status of this application or proceeding should be directed to Kim Downing for Art Unit 1642 whose telephone number is 571-272-0521

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Jeffrey Siew can be reached on 571-272-0787. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Lei Yao, Ph.D.
Examiner
Art Unit 1642

LY

SHEELA HUFF
PRIMARY EXAMINER